Claims 1-16 were pending in the application and stand rejected. By the present amendment, claims 7 and 12 have been cancelled. Currently, claims 1-6, 8-11, and 13-16 are pending, of which, claims 1, 9, and 14 are independent.

Reconsideration of this Application is respectfully requested in light of the foregoing amendments and the following remarks. References discussed in the following remarks are being supplied in an Information Disclosure Statement.

Rejections Under 35 U.S.C. §112, First Paragraph

At page 2 of the Office Action, claims 7 and 12 stand rejected under 35 U.S.C. §112, first paragraph. By the present amendment, claims 7 and 12 have been cancelled. Accordingly, the rejection of claims 7 and 12 is now moot.

Rejections Under 35 U.S.C. §102

At page 3 of the Office Action, Claims 1-4 and 6-16 stand rejected under 35 U.S.C. §102(b) based upon a public use or sale of the invention based on breast-feeding. The Office Action states that leptin is present in breast milk and is present in whole milk as evidenced by Applicant's publication (Smith-Kirwin et al., Journal of Clinical Endocrinology and Metabolism, May 1998). Based on this, the Examiner takes the position that leptin is naturally administered orally to infants who are breast fed and who may be premature and have impaired surfactant production and respiratory distress syndrome or Bronchopulmonary Dysplasia. For the reasons below, Applicant respectfully disagrees.

It is important to point out that the leptin levels measured in Applicant's publication were measured in established breast milk in which the mother delivered full-term infants, not premature infants. This is important because the level of leptin in

premature breast milk is significantly lower than leptin levels in established breast milk. Resto et al. (2001) reported leptin levels in premature breast milk as 5.28+/- 24.79 compared to the levels reported in established breast milk 73.22 +/- 39.08. This data coupled with the finding that small-for gestational age infants show only a marginal increase (23%) in serum leptin levels after breast feeding, whereas appropriate-for-gestational age and large-for-gestational age infants demonstrate much larger increases of 47% and 136%, respectively (Cinaz et al., 1999) leads to the conclusion that when a mother breast feeds a premature infant, the mother's premature breast milk does not have sufficient leptin levels that would amount to administering a leptin compound to the individual for a time and in an amount sufficient to enhance surfactant production as required in claims 1, 9, and 14. This conclusion is substantiated by the study of Spear et al. (2001) in which it is shown that serum leptin levels are low in premature infants and remain low during the duration of the premature infants' hospitalization despite adequate nutrition, including breast feeding.

Accordingly, Applicant maintains that claims 1, 9, and 14 are not anticipated by breast-feeding an infant. Claims 2-6, 8, 10-11, 13, and 15-16 are dependent claims that depend from either claim 1, 9, or 14 and are likewise not anticipated by breast-feeding an infant.

Rejections Under 35 U.S.C. §103

At page 4 of the Office Action, Claims 1-16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Torday et al., FASEB Journal, March 15, 2000, Vol. 14, No. 4, and/or Torday et al., Pediatric Research, 378A, March 2000, and further in

view of Griese, European Respiratory, Journal, 1999, and Halliday et al., In: Hot Topics in Neonatology, 1999, and O'Donnell et al., Am. J. Resp. Crit. Care Med 159, 1999.

Based on these five references, the Examiner takes the position that it would have been prima *facie obvious* to increase the production of lung surfactant in respiratory conditions in which individuals have impaired surfactant production, by treatment with leptin, as taught by Torday et al. because, Halliday teaches that treatment with corticosteroids has not been proven effective and has serious side effects, and because Griese teaches that there are a number of respiratory diseases in which lung surfactant is deficient and needs to be enhanced or replaced. The Examiner further contends that there would be a reasonable expectation of success, since O'Donnell et al. teaches enhancement of respiratory function by exogenous treatment with leptin, though the mechanism of enhancement was not known.

First, as pointed out by the Examiner, Griese and Halliday et al. show a need for alternative treatments to increasing lung surfactant production. However, these references do not show, teach or suggest that administering leptin to an individual will *enhance surfactant production* in an individual as required by claims 1, 9, and 14.

Turning now to the O'Donnell et al. reference, O'Donnell et al. show that leptin acts centrally at the level of hypothalamic control centers in the brain to control respiration and ventilation. Importantly, there is no evidence for leptin acting peripherally on other tissues, like lung tissues, to control respiratory function. Further, O'Donnell did not examine the effects of leptin on immature lung tissue as seen in premature infants with RDS nor in adults with insufficient or low surfactant levels as found in adult cases with RDS. Accordingly, O'Donnell does not disclose, teach or

suggest that leptin may be administered to an individual to *enhance surfactant production* as required by claims 1, 9, and 14.

This deficiency is not cured by the Torday et al. references. Torsday et al. show that leptin increases phosphatidylcholine levels in an established lung cell line. They do not show that leptin increases the levels of surfactant proteins A, B, and C. Further, they do not demonstrate that leptin increases phosphatidylcholine levels in an animal model nor in lung cells or tissue with insufficient production of surfactant as would be found in premature infants with RDS or in adults with ARDS. Furthermore, it has been demonstrated that the genes encoding the surfactant proteins are regulated independently from each other and from the genes responsible for regulating phospholipid synthesis (Mendelson and Boggaram, 1991; Rooney, Young, and Mendelson, 1994; Whitsett et al., 1995). For example, insulin has been shown to increase phospholipid production, yet decrease the levels of surfactant protein A and increase the incidence of RDS. In addition, animal models in which the surfactant proteins have been knocked out all demonstrate RDS and fail to survive. Also, surfactant preparations that lack the surfactant proteins are more efficacious in the prevention and treatment of RDS in prematurely born infants than are the synthetic phospholipids mixtures. Neither Torday et al. or O'Donnell et al. either alone or in combination, discloses, teach, or suggest that leptin may be administered to an individual to enhance lung surfactant production as required by claims 1, 4, and 9.

Accordingly, Applicant respectfully contends that claims 1, 4, and 9 are not obvious over Torday et al., Griese, Halliday et al., or O'Donnell et al. either alone or in combination with one another. Claims 2-6, 8, 10-11, 13, and 15-16 are dependent claims

that depend from either claim 1, 9, or 14 and are likewise not obvious over Torday et al., Griese, Halliday et al., or O'Donnell et al.

Conclusion

Applicant respectfully submits that the foregoing remarks demonstrate that the present application is in condition for allowance. All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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